Statins and primary prevention of venous thromboembolism: systematic review and meta-analysis of prospective cohort and randomised intervention studies

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Summary

Background Statins have been suggested to have a protective effect on venous thromboembolism (VTE) (which includes deep vein thrombosis and pulmonary embolism), but the evidence is uncertain. We sought to evaluate the extent to which statins are associated with first VTE outcomes.

Methods We conducted a systematic review and meta-analysis of observational cohort studies and randomised controlled trials (RCTs). Relevant studies which reported associations between statins and first VTE outcomes were identified from MEDLINE, EMBASE, Web of Science, Cochrane Library, manual search of bibliographies to July 2016, and email correspondence with investigators. Study specific relative risks (RRs) with 95% confidence intervals were aggregated using random effects models and were grouped by study level characteristics. The review has been registered in the PROSPERO prospective register of systematic reviews (CRD42016035622).

Findings There were 36 eligible studies (13 cohort studies comprising 3 148 259 participants and 23 RCTs of statins versus placebo or no treatment, comprising 118 464 participants). In observational studies, the pooled RR for VTE was 0·75 (0·65-0·87) when comparing statin use with no use. This association remained consistent when grouped by various study level characteristics. In RCTs, the RR for VTE was 0·85 (0·73-0·99) comparing statin therapy with placebo or no treatment. Subgroup analyses suggested significant differences in the effect of statins by type of statin, with rosuvastatin having the lowest risk on VTE compared to other statins 0·57 (0·42-0·75). There was no evidence of an effect of statin use on pulmonary embolism.

Interpretation Available evidence from observational and intervention studies suggest a beneficial effect of statin use on VTE. In intervention studies, therapy with rosuvastatin significantly reduced VTE compared to other statins. Further evidence is however needed to validate these findings.

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Keywords statin; venous thromboembolism; venous thrombosis; pulmonary embolism; primary prevention; systematic review; meta-analysis

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE) is a public health problem. Although pharmacologic thromboprophylaxis agents (such as unfractionated heparin, low-molecular-weight heparins, warfarin, and novel oral anticoagulants) are effective, they remain underused, because they are associated with increased risk of bleeding.(1) The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (commonly known as statins), are known for their lipid-lowering properties and well established for the primary and secondary prevention of cardiovascular disease (CVD),(2-4) especially coronary heart disease.(5) Statins are also known to have pleiotropic effects that affect coagulation and inflammation, and do not increase bleeding risk.(6, 7) There is emerging evidence to suggest that through these pleiotropic effects, statins may be effective in reducing the incidence of VTE. Since the publication of the Heart and Estrogen/progestin Replacement Study (HERS), which reported an approximately 50 percent risk reduction in VTE in a nonrandomised comparison of statin versus nonstatin users,(8) several observational studies have evaluated this relationship and reported conflicting results.(9-13) In the first randomised controlled trial (RCT) of statins for the prevention of VTE, investigators of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial of 17 802 participants, demonstrated that rosuvastatin significantly reduced the occurrence of all cases of VTE.(14) These results were based on relatively few VTE events suggesting a statistical play of chance and thus triggered calls for further studies to replicate these results.(15) With the publication of these studies, there have been efforts to aggregate these data over the last decade and which have resulted in a number of published reviews on the topic with inconsistent results.(16-19) In analysis of eight case-control studies and three cohort studies, Squizzato and colleagues showed no evidence of a significant reduction in VTE with statin use, when the results were pooled by study design; however, pooled analysis of all studies (including the JUPITER trial) showed a significant reduction in risk of VTE.(17) In a meta-analysis of 29 RCTs published in 2012, Rahimi and colleagues found no significant reduction in VTE events with statin therapy.(19)

Indeed, the existing evidence shows there is still uncertainty regarding the effect of statins on VTE outcomes. In addition, there were several features of these previous reviews which limited the generalisability and validity of the findings. First, majority of these previous reviews (except for the study by Rahimi and colleagues(19)) pooled a limited number of studies which did not provide adequate power to evaluate the associations. Second, several of these reviews pooled results of different study designs making interpretation of the findings difficult. Third, these previous reviews did not conduct detailed exploration of potential sources of heterogeneity among the contributing studies using formal tests such as subgroup analyses and meta-regression techniques. The topic is under considerable debate and of clinical interest as an increasing number of people are being prescribed statin therapy; and given the publication of newer studies since the last relevant meta-analysis on the topic, there is a need for further work to address the persisting uncertainties on the role of statins on VTE outcomes. In this context, we aimed to summarise the available observational and interventional evidence in one updated systematic meta-analysis. Our objectives were to (i) determine the associations of statin use with risk of first VTE outcomes in observational cohort studies; (ii) quantify the effects of statin use given alone compared with placebo (or no treatment) for the primary prevention of VTE outcomes in RCTs; and (iii) examine all associations under a wide range of relevant study level characteristics.

Methods

Data sources and search strategy

We conducted this review using a predefined protocol, which has been registered in the PROSPERO prospective register of systematic reviews (CRD42016035622), and in accordance with PRISMA and MOOSE guidelines(20, 21) (Pages 2-5 of SUPPLEMENTARY MATERIAL). Two authors independently sought studies published before July, 2016 (date last searched) using MEDLINE, EMBASE, Web of Science, and the Cochrane electronic databases. The computer-based searches combined terms related to statins (e.g., *statin, hydroxymethylglutaryl-CoA reductase inhibitors, atorvastatin, simvastatin*) and outcomes (e.g., *venous thromboembolism, deep vein thrombosis, pulmonary embolism*) in humans, without any language restriction. Details on the search strategy are provided in Page 6 of SUPPLEMENTARY MATERIAL. Two reviewers working independently screened the titles and abstracts of all initially identified studies according to the selection criteria. Full texts were retrieved from studies that satisfied all selection criteria. Reference lists of selected studies and relevant reviews identified on the topic were manually scanned for additional publications.

Study selection and eligibility criteria

Observational cohort (prospective cohort, retrospective cohort, or nested case-control) studies were eligible for inclusion if they assessed the association of any or current statin use with first VTE, DVT, or PE event (as detected by imaging using venous ultrasonography, venography, angiography, computed tomography, ventilation and perfusion scan, or any other recognised confirmatory tests) in adults (≥ 18 years old). Intervention studies were eligible if they were randomised controlled, open or blinded trials; assessed the effects of statin therapy compared to a placebo or no treatment in adults; and collected VTE outcomes. Studies were excluded if they were non-randomised comparing statin with another statin or lipid-lowering agent or were secondary publications of trials already included in the analysis. In addition, case-control studies and studies that reported the associations between statin therapy and recurrent VTE were excluded.

Data extraction

Two authors (SKK and SS) independently extracted data and a consensus was reached in case of any inconsistency with involvement of a third (KK). We used a predesigned data extraction form to obtain relevant information. These included study-level information on study design; baseline population including proportion of men; location; average age at baseline; numbers enrolled and randomised; allocation concealment; blinding; statin type and dosage; duration of treatment or follow-up; degree of adjustment for potential confounders (defined as '+' when RRs were adjusted for age and/or sex; '++' further adjustment for established risk factors for VTE such as body mass index, history of diabetes, smoking status, exercise, alcohol consumption, immobilization, ; and '+++' additional adjustment for other potential confounders such as estrogen use or use of anticoagulants); treatment comparisons; and nature of outcome and numbers. Venous thromboembolism outcomes were extracted as reported by the eligible studies. The primary outcome of this analysis was VTE which was reported by majority of studies. Data on the specific endpoints of DVT and PE were also extracted when reported. We extracted risk estimates reported for the greatest degree of adjustment. If risk estimates were unavailable from a published report, we collected relevant data by abstracting from other published reviews or by contacting investigators of these published studies. In the case of multiple publications involving the same study, the most up-to-date or comprehensive information was abstracted.

Assessing the risk of bias

For observational cohort studies, we used the nine-star Newcastle–Ottawa Scale (NOS),(22) which is based on pre-defined criteria namely: selection (population representativeness), comparability (adjustment for confounders), and ascertainment of outcome. The NOS assigns a maximum of four points for selection, two points for comparability, and three points for outcome. Nine points on the NOS reflects the highest study quality. For RCTs, we used the Cochrane Collaboration's risk of bias tool.(23) This tool evaluates seven possible sources of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. For each individual domain, studies were classified into low, unclear and high risk of bias.

Statistical analysis

Summary measures were presented as relative risks (RRs) with 95% confidence intervals (CIs). Following Cornfield's rare disease assumption,(24) hazard ratios and odds ratios were assumed to approximate the same measure of RR. When studies published more than one estimate of the association according to subgroups (e.g., by sex, dosage), we obtained a within-study summary estimate using a fixed effect meta-analysis. The inverse variance weighted method was used to combine summary measures using random-effects models to minimise the effect of between-study heterogeneity.(25) Subsidiary analyses employed fixed effects models. Statistical heterogeneity across studies was quantified using the Cochrane χ^2 statistic and the I^2 statistic.(26) Study-level characteristics [such as geographical location, study design, baseline population (general populations versus populations with pre-existing disease or at high VTE risk), allocation concealment, statin class, statin dosage (high versus low dose), source of data (for RCTs), and study quality] were pre-specified for assessment of heterogeneity, which was conducted using stratified analyses and random effects meta-regression.(27) In analysis specified post-hoc which was based on distribution of available data, further stratified analysis was conducted to examine the difference in pooled RRs by baseline average age of participants, duration of follow-up or treatment, and number of outcomes. We assessed the potential for publication bias through formal tests, namely Begg's funnel plots and Egger's regression symmetry tests.(28) All statistical tests were two-sided and used a significance level of $P<0.05$ and STATA release 14 (StataCorp LP, College Station, TX, USA) software was used for all statistical analyses.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Study identification and selection

Our initial search of relevant databases and manual scanning of reference lists identified 1125 potentially relevant citations. After screening based on titles and abstracts, 54 articles remained for full text evaluation. Following detailed assessments, 18 articles were excluded because (i) they were based on reviews (n = 8); (ii) they were case-control studies (*n* = 7); or evaluated recurrent outcomes (*n* = 3) (Pages 7-8 of SUPPLEMENTARY MATERIAL). The remaining 36 studies met our inclusion criteria and were included in the meta-analysis (figure 1; Pages 9-16 of SUPPLEMENTARY MATERIAL). Table 1 provides summary characteristics of relevant observational cohort studies and RCTs included in the meta-analysis.

Study characteristics and quality

Pages 9-10 of SUPPLEMENTARY MATERIAL provides details of the key characteristics as well as quality assessment scores of observational cohort studies included in the review. In aggregate, there were 13 studies (published between 2001 and 2014) involving 3 148 259 participants and 49 117 VTE outcomes. Twelve studies reported on VTE (3 022 397 participants; 49 117 events), two on DVT (142 412 participants; 4513 events), and one on PE (16 550 participants; 3006 events). Except for one study with an average follow-up of 30 days for VTE outcomes, the median (interquartile range) duration of follow-up was 4·6 (2·6-7·4) years. Of these observational cohort studies, eight involved participants from Europe (UK, Finland, Austria, and Netherlands), three from North America (USA and Canada), and two from Asia (Saudi-Arabia and Israel). Quality scores of the studies ranged from 5 to 8.

A total of 23 RCTs involving 118 464 participants and 1031 VTE outcomes were included in the review (table 1 and Pages 11-13 of SUPPLEMENTARY MATERIAL). Some baseline data and risk estimates for VTE outcomes in 20 of these trials were extracted from a published review,(19) because these data had not been reported in the original articles. Rahimi and colleagues obtained these data from investigators of these trials and have appropriately acknowledged this in their review. We have also verified this by contacting authors of these published studies. The majority (n=17) of trials were double-blinded and six were open label trials. Majority of trials were conducted multinationally or within the European region (Scotland, Ireland, The Netherlands, Germany, and Italy). The baseline age of participants ranged from 18 to 90 years. Included trials employed different types of statin (artovastatin, fluvastatin, lovastatin, pravastatin, simvastatin, or rosuvastatin) with dosages ranging from 10 mg to 80 mg daily and the median (interquartile range) duration of follow-up was 3·9 (2·5-5·0) years. Using the Cochrane Collaboration tool, only six trials demonstrated a high risk of bias within one area of study quality, which was blinding of participants and personnel. All trials had a low risk of bias in random sequence generation and had an unclear risk of bias in one or more areas of study quality (Page 17 of SUPPLEMENTARY MATERIAL). There was considerable variability in study populations for both observational cohort studies and RCTs, which included participants recruited from general populations, participants at high vascular risk, participants with pre-existing conditions such as diabetes, heart failure, cancer, as well as renal transplant patients and patients with mild to moderate Alzheimer's disease. All studies reported on the use of statin for the primary prevention of VTE outcomes.

Association of statin use with VTE in prospective cohort studies

Figure 2 presents RRs for VTE outcomes for statin use compared with no statin use in observational cohort studies contributing to pooled analysis. A significant reduction in risk of VTE was found with statin use compared with no statin use 0·75 (95% CI: 0·65 to 0·87; p<0·0001). In sensitivity analyses, the combined RR excluding the study with less than one year follow-up was 0·75 (0·65-0·87; p<0·0001), which was identical to the main finding. There was evidence of substantial heterogeneity between the contributing studies (I^2=82%, 70 to 89%; p<0·0001) which was partly explained by several study level characteristics such as geographical location (p for meta-regression = 0·014), study design (p for meta-regression = 0·001), baseline population (p for meta-regression < 0·0001), study size (p for meta-regression < 0·0001), and study quality (p for meta-regression = 0·026). A stronger association was observed in populations with pre-existing disease or at high VTE risk 0·46 (95% CI: 0·25 to 0·83; p=0·010) compared to studies that recruited participants from the general population 0·86 (95% CI: 0·80 to 0·92; p<0·0001) (figure 3). In further exploration of heterogeneity, this was substantially reduced when pooled analysis was limited to prospective cohort designs (I^2=58%, 8 to 81%; p=0·020) and the pooled result was attenuated but a protective association was still evident 0·88 (0·81-0·96; p=0·004). Similar results were observed when analysis was limited to studies that recruited participants from general populations.

Statin use compared to no statin use was also associated with a significant reduction in risk of the specific endpoint of DVT 0·77 (95% CI: 0·69 to 0·86; p<0·0001). There was no evidence of heterogeneity between the two studies included in this analysis. In one study reporting PE outcomes, the RR for PE comparing statin use with no statin use was 1·02 (95% CI: 0·74 to 1·40; p=0·90).

Effects of statin therapy on VTE in randomised controlled trials

Statin therapy compared with placebo or no treatment, was associated with a significant reduction in risk of VTE events in pooled analysis of 23 trials 0·85 (95% CI: 0·73 to 0·99; p=0·038) (figure 4). There was no evidence of substantial heterogeneity between the contributing studies (I^2=13%, 0 to 47%; p=0·28). The pooled RR remained unchanged using a fixed effects model 0·85 (95% CI: 0·73 to 0·99; p=0·032). In subgroup analyses, the effect of statin therapy on VTE risk did not vary significantly across several study level characteristics, except for by statin class (p for meta-regression = 0·015). Populations on rosuvastatin therapy had a significant reduction in VTE events compared to other statins. The risk of VTE was statistically significantly reduced for general populations compared to populations with pre-existing disease or at high risk of VTE. Similarly, compared to high dose artovastatin or rosuvastatin, low doses of each of these statins were associated with a statistically significant reduced risk of VTE (figure 5). In the single largest trial that also reported results for the specific endpoints of DVT and PE; whiles a significant reduction in risk of DVT was found for statin therapy, there was no significant effect on PE (figure 4).

Publication bias

Under visual examination, funnel plots for both observational cohort studies and RCTs were symmetrical and Egger's regression tests showed no statistical evidence of publication bias (Page 18 of SUPPLEMENTARY MATERIAL).

Discussion

Key findings

The findings of this review indicate a protective effect of statin use in the primary prevention of VTE in both observational cohort and intervention studies. The inverse association demonstrated in observational studies remained consistent across several study level subgroups. In RCTs, there was suggestion of effect modification in stratified analyses by type of statin. Rosuvastatin therapy substantially and significantly reduced VTE risk, with no benefit seen with other statins. There was no evidence of a protective effect of statins on the specific outcome of PE in both observational cohort and intervention studies.

Comparison with previous work

A number of reviews have been conducted on the topic and some of our findings concur with those of these previous reviews. In a meta-analysis of 10 studies (comprising one RCT and a mixture of case-control, retrospective, and prospective cohort studies), Agarwal and colleagues reported a decreased risk of VTE outcomes with statin use.(16) Pai and colleagues in pooled analysis of four case-control and four cohort studies showed a statistically significant reduction in risk of VTE.(18) In agreement with the results of these previous reviews, our pooled analysis of observational studies demonstrated a significant reduction in risk of VTE. However, our updated review of observational cohort studies also provides several important findings that have not been previously reported. Based on inclusion of additional studies, we had enhanced power to examine the associations in greater depth, such as the detailed exploration of sources of heterogeneity using a broader range of individual and study level circumstances. Our analyses suggested differences in the effect of statin use on VTE events by characteristics such as geographical location, study design, baseline population, and study size. Our review of RCTs provide several relevant findings that were not previously reported by the last relevant review published on the topic.(19) We found a significant reduction in VTE in pooled analysis of 23 RCTs of statin therapy compared with placebo or no treatment. Stratified analyses by several study level characteristics suggested evidence of effect modification by statin type, with rosuvastatin showing a beneficial effect on VTE compared to other statins. There were also suggestions of differences in the effect of statin on VTE by baseline population and statin dose; however, there was no statistically significant evidence of effect modification in these analyses.

Possible explanations for findings

The statistically significant findings in our pooled analyses of RCTs are not in stark contrast to findings of Rahimi and colleagues.(19) The risk estimate reported in the previous review was consistent with a potential benefit of statin on VTE, but was on the verge of statistical significance. This could be attributed to low power to detect an effect. The addition of results of a new and larger trial to the pooled evidence may have resulted in enhanced power to show a significant risk reduction in VTE. Our findings from both observational and interventional evidence do suggest that statins may indeed have a protective effect on VTE. Statins in addition to their lipid-lowering properties are known to have several vascular protective effects which are independent of changes in cholesterol profiles, and these have been attributed to anti-inflammatory and antithrombotic properties; alteration of endothelial dysfunction which leads to increased nitric oxide production; and regulation of angiogenesis.(29) Factors implicated in the pathogenesis of VTE include endothelial dysfunction, alterations in blood flow, and hypercoagulable states.(30) Given the major role of the coagulation cascade in the development of VTE, several related mechanisms have been postulated for the protective effect of statins on risk of VTE. First, growing evidence from both human studies and animal models suggest that statins downregulate the blood coagulation cascade, leading to reduced tissue factor expression, which causes reduced thrombin formation.(31-34) Second, statins via increased expression of thrombomodulin on the endothelial cells, may enhance the activity of the protein C anticoagulation system, which inhibits the coagulation cascade.(35) Third, statins also decrease the susceptibility for thrombosis and coagulation, by decreasing plasminogen activator inhibitor-1 expression(36) and increasing tissue plasminogen activator. In addition, profibrinolytic and antiplatelet properties have also been reported.(29, 37) Statins have been shown to modulate fibrin clot properties in both healthy individuals and those with previous VTE.(38) A recent review has also suggested that the antithrombotic effects of statins are likely to be linked to their anti-inflammatory properties.(39)

Whether VTE reduction is a class effect of statins is uncertain given the existing limited and inconsistent evidence.(12, 40) In our subgroup analyses of RCTs, we found evidence suggesting a difference in the effect of statin on VTE by type of statin, with rosuvastatin having a significant beneficial effect on risk of VTE compared to other statins. However, given that we were unable to conduct a head-to-head comparison of the statins and the limited number of studies available for such subgroup analyses, these findings may have arisen from the effects of low statistical power or chance. Further investigation is therefore needed to replicate and validate these results.

Implications of our findings

Several implications exist for our findings. Based on both observational and clinical trial evidence, these findings underscore a potential beneficial role of statin therapy on VTE in addition to its established role in CVD prevention. The results also suggest that this effect of statins may be attributed to rosuvastatin. Currently, statins are only approved for lipid lowering in the primary and secondary prevention of CVD;(41) however, they have shown great promise beyond their established lipid-lowering effects and these include potential beneficial impact on multiple disease conditions.(42) In addition, statins have a good safety profile, are affordable, and widely used. These results provide an extensive body of evidence on the clinical benefit of statin in the occurrence of VTE and may support a true protective effect. Venous thromboembolism affects several millions of people globally and is one of the most preventable causes of hospital deaths.(43) Prevention of VTE may be another potential indication of statins; however, before any guideline recommendations should be made, further research is needed to unequivocably establish this potential true protective effect. In addition, the role of statins in the secondary prevention of VTE is of emerging clinical interest. However, only a limited number of studies have explored the effect of statins on VTE recurrence and the results have mostly been based on administrative data and are conflicting.(44, 45) In a post-hoc analysis of the EINSTEIN DVT and PE study, there was no statistically significant reduction in the risk of recurrent VTE comparing statin-users with non-users.(46) Further investigation is also required to evaluate the putative preventive effect of statins in VTE recurrence.

Strengths and limitations

Our systematic review and meta-analysis has several strengths in comparison to previous reviews and these deserve mention. Our review included analyses of observational evidence as well as clinical trial data in a single investigation; thus providing the most comprehensive update on the effect of statin therapy on VTE. Our search strategy was very detailed, was without language restriction, and spanned multiple databases. Most of our trial evidence was based on unpublished data which was recently published by a recent elegant review.(19)

Indeed, formal tests showed no evidence of publication bias in our analyses. The generalisability of our findings was enhanced by the involvement of data from 13 observational studies and 23 RCTs, making it the largest review to date on the topic. There was enhanced power, therefore the ability to quantify more reliably the magnitude of the associations as well as conduct detailed analyses under a wider range of study-level circumstances. Given the data available, we were able to systematically explore possible sources of heterogeneity using stratified and meta-regression analyses. A detailed assessment of methodological quality of the included studies was conducted; observational cohort studies were all of adequate quality and majority of the intervention studies had low risk of bias. In our review of observational evidence, we included only observational cohorts, which offsets some of the biases inherent in cross-sectional and case-control studies and decreases the likelihood of reverse causality. Finally, our results remained robust in several sensitivity analyses. There are several limitations which also deserve consideration. First, owing to the small number of studies (both observational studies and RCTs) for the outcomes of DVT and PE, this precluded inadequate assessment of the impact of statin use or therapy on each of these endpoints. Second, due to the limited data available for subgroup analyses by statin type in both study designs, we were unable to adequately explore whether the effect of statins on VTE was a class effect. Third, we pooled estimates from both retrospective and prospective cohort designs as well studies that included people from the general population and those at high risk of thrombotic events, which could have potentially led to biased estimates. The lack of appropriate data precluded the ability to compare the protective effect of statins in participants with normal cholesterol levels to those with hypercholesterolemia. However, our results of a subgroup analyses by the type of study design and baseline population showed a protective effect of statin use on VTE in all groups. Fourth, we were unable to conduct a subgroup analysis by type of VTE (provoked versus unprovoked) because of limited data provided by eligible studies. Fifth, as with aggregate data, pooled analysis of observational cohorts was based on variably adjusted data reported by the eligible studies, thereby increasing the possibility of residual confounding. However, all studies adjusted for a comprehensive panel of biological markers and lifestyle characteristics. Sixth, there was substantial heterogeneity between observational studies, however possible sources of this were systematically explored using stratified and meta-regression analyses. There was however no significant evidence of heterogeneity between the contributing trials. Finally, given that our trial evidence was mostly based on previously unpublished data (with VTE collected as adverse events) contributed by investigators, this could have potentially led to biased estimates in our analyses. However, a subgroup analysis comparing pooled estimates from previously unpublished data to published data (where VTE was pre-specified as an outcome) showed no evidence of effective modification. Given the limitations, the findings should be interpreted with caution and intensify the need for detailed future intervention studies with VTE pre-specified as primary outcomes and individual patient data meta-analysis to help establish the beneficial role of statins in the prevention of VTE.

Conclusions

Available evidence from observational and intervention studies suggest a beneficial effect of statin use on VTE. Therapy with rosuvastatin significantly reduced VTE compared to other statins. Further research may be required to validate the beneficial effect of statin therapy on VTE and establish if there is a class effect of statins on VTE.

Contributors: SKK, SS, and KK conceived and designed the study. SKK, SS, and KK acquired data. SKK analysed and interpreted the data. SKK drafted the manuscript. SKK, SS, and KK critically revised the manuscript for important intellectual content. KK supervised the study.

Declaration of interests

SS has received honoraria for speaking at meetings and serving on Advisory Boards for Novartis, Novo Nordisk, Janssen, MSD, Lilly and BI. KK has acted as a consultant and speaker for Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp &

Dohme, Janssen and Boehringer Ingelheim. He has received grants in support of investigator and investigator initiated trials from Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim and Merck Sharp & Dohme and Roche. KK has served on advisory boards for Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Janssen and Boehringer Ingelheim.. SKK has no conflict of interest.

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Research in context

Evidence before this study
The lipid-lowering properties of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (commonly known as statins) and their effectiveness for the primary and secondary prevention of cardiovascular disease (CVD) are well established. Statins are currently only approved for lipid lowering in the primary and secondary prevention of CVD. Relevant prospective cohort studies conducted in general populations and randomised controlled trials (RCTs) reporting on associations between statins and venous thromboembolism (VTE) (including deep vein thrombosis and pulmonary embolism) were sought from MEDLINE, EMBASE, Web of Science, and Cochrane Library; with particular emphasis on systematic reviews and meta-analyses of these study designs. We used the search terms "statin", "hydroxymethylglutaryl-CoA reductase inhibitors" and "venous thromboembolism", "deep vein thrombosis", "pulmonary embolism". Several observational studies were found to have evaluated the relationship, but the results were conflicting. A limited number of RCTs demonstrated that

statins reduced the occurrence of VTE, but these results were based on few VTE events, which suggested a statistical play of chance. Previous reviews on the topic have also reported inconsistent results. Statins may have a protective effect on the incidence of VTE, however, the overall evidence is uncertain.
Added value of this study
This meta-analysis of observational and intervention studies suggest a beneficial effect of statin therapy on venous thromboembolism. In observational studies, the protective effect of statins on risk of VTE remained consistent when grouped by various study level characteristics. In intervention studies, rosuvastatin therapy substantially and significantly reduced the risk of venous thromboembolism risk, with no benefit seen with other statins.
Implications of all the available evidence
Based on both observational and clinical trial evidence, these findings underscore a potential beneficial role of statin therapy on VTE in addition to its established role in CVD prevention. The results also suggest that this effect of statins may be attributed to rosuvastatin. Prevention of VTE may be another potential indication of statins; however, before any guideline recommendations should be made, further research is needed to unequivocably establish this potential true protective effect.

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Figure Legends

Figure 1: **PRISMA flow diagram**

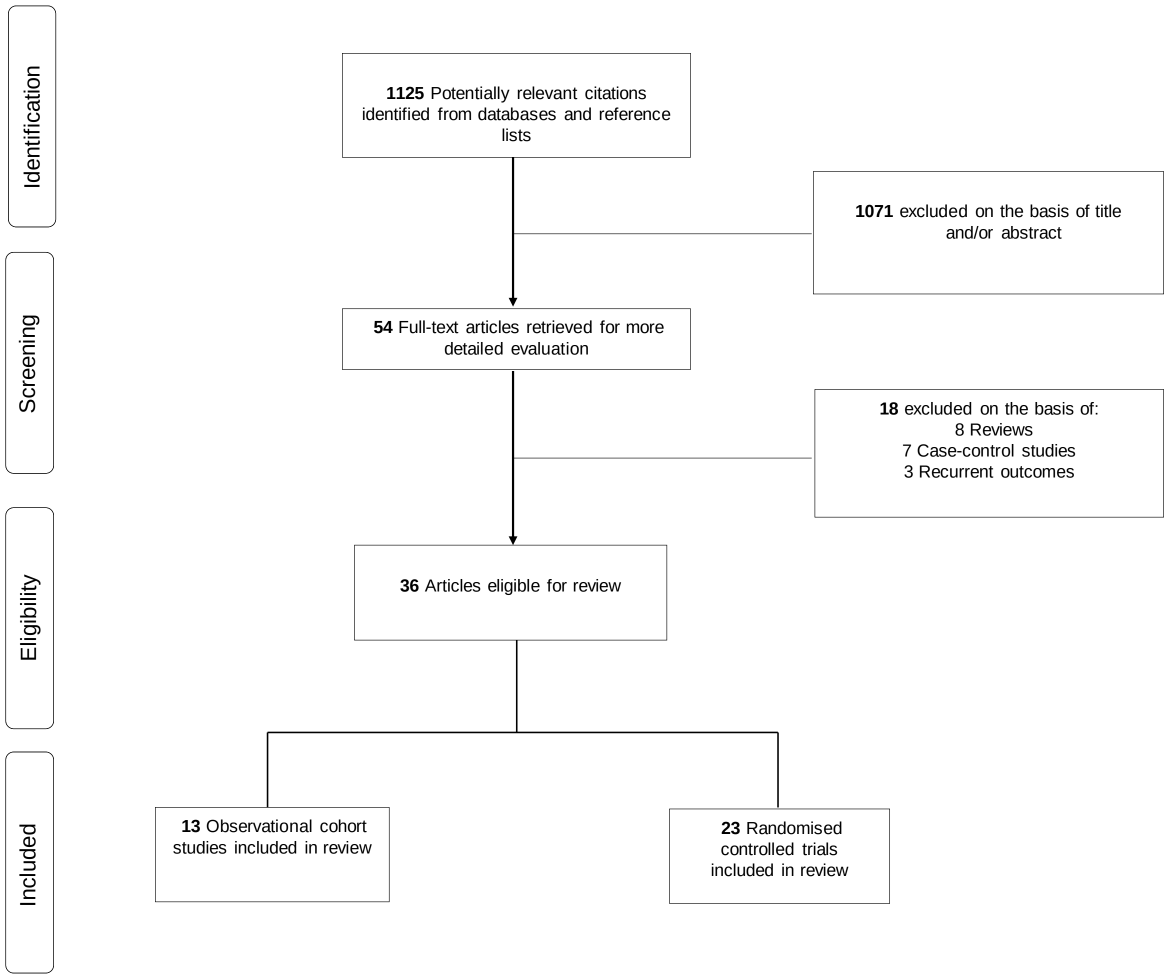
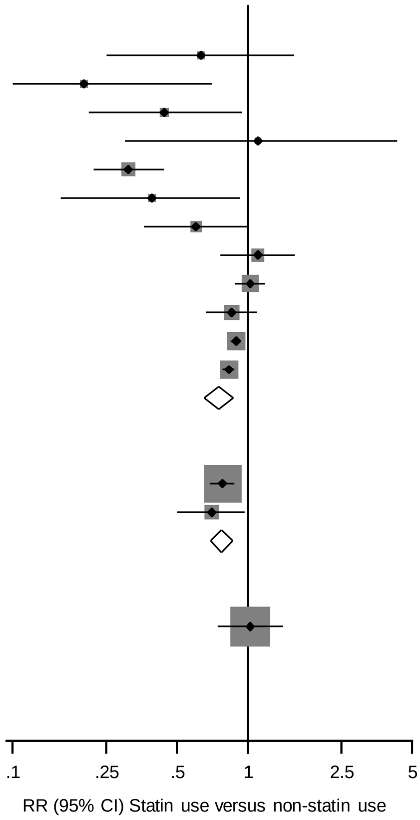


Figure 2: **Association of statin use with risk of venous thromboembolism in observational cohort studies**

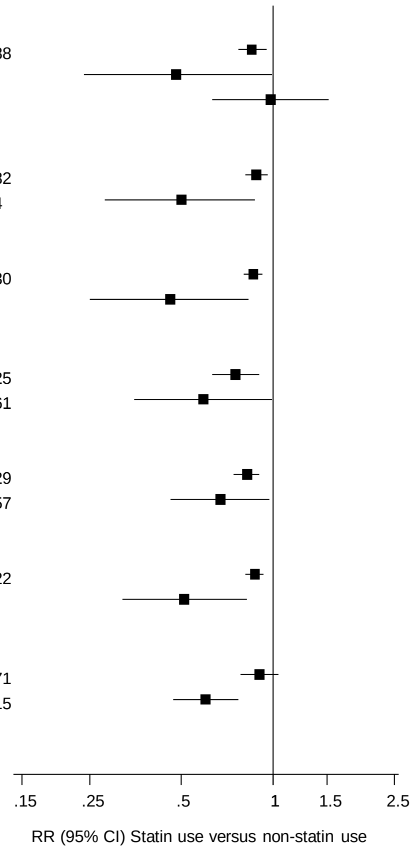
Author, year of publication	No. of participants	No. of cases	RR (95% CI)
Venous thromboembolism			
Harbi, 2013	798	6	0.63 (0.25, 1.57)
Resh, 20	289	20	0.20 (0.10, 0.70)
Herrington, 2002	2763	41	0.44 (0.21, 0.94)
Yang, 2002	504	72	1.10 (0.30, 4.30)
Khemasuwan, 2011	1100	107	0.31 (0.22, 0.44)
Lotsch, 2014	1434	107	0.39 (0.16, 0.92)
Lassila, 2014	7925	136	0.60 (0.36, 1.00)
Shai, 2014	1746	175	1.10 (0.76, 1.58)
Smeeth, 2009	729529	6199	1.02 (0.88, 1.18)
Huerta, 2007	16550	6550	0.85 (0.66, 1.09)
Hippisley-Cox, 2010	2004692	12199	0.89 (0.84, 0.93)
Fournier, 2014	255067	23505	0.83 (0.78, 0.87)
Subtotal	**3022397**	**49117**	**0.75 (0.65, 0.87)**
Deep vein thrombosis			
Ray, 2001	125862	969	0.78 (0.69, 0.87)
Huerta, 2007	16550	3544	0.70 (0.50, 0.97)
Subtotal	**142412**	**4513**	**0.77 (0.69, 0.86)**
Pulmonary embolism			
Huerta, 2007	16550	3006	1.02 (0.74, 1.40)



CI, confidence interval (bars); RR, relative risk

Figure 3: **Association of statin use and venous thromboembolism in observational cohort studies, grouped according to several study characteristics**

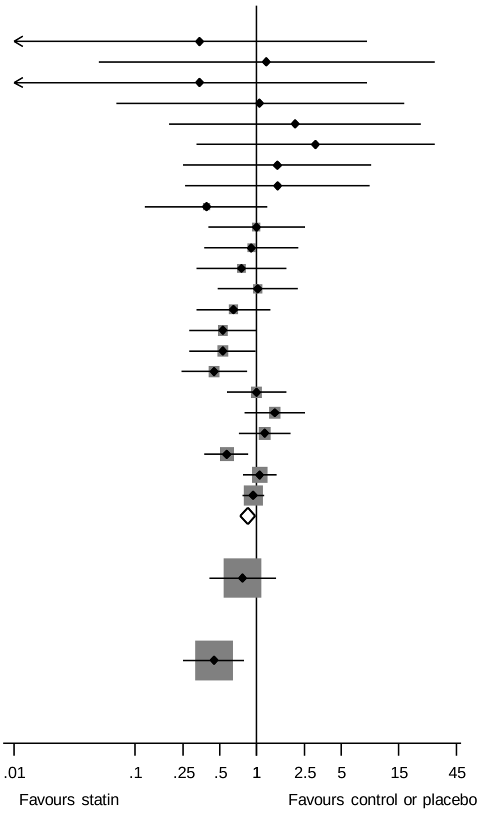
Subgroup	No. of participants	No. of VTE cases	RR (95% CI)	*P*-value*
Location				
Europe	3 015 990	48 788	0.85 (0.77, 0.95)	0.014
North America	129 725	1117	0.48 (0.24, 0.99)	
Asia	2544	181	0.98 (0.63, 1.52)	
Design				
Prospective cohort	3 012 579	48 782	0.88 (0.81, 0.96)	0.001
Retrospective cohort	135 680	1,304	0.50 (0.28, 0.87)	
Baseline population				
General population	3 140 129	49 630	0.86 (0.80, 0.92)	< 0.001
Population at high VTE risk	8130	456	0.46 (0.25, 0.83)	
Average baseline age, yrs				
≥ 60	1 134 555	37 725	0.75 (0.63, 0.90)	0.628
< 60	2 013 704	12 361	0.59 (0.35, 0.99)	
Average follow up, yrs				
> 5	2 393 835	36 829	0.82 (0.74, 0.90)	0.665
≤ 5	754 424	13 257	0.67 (0.46, 0.97)	
No. of events				
≥ 500	3 131 700	49 422	0.87 (0.81, 0.93)	< 0.001
< 500	16 559	664	0.51 (0.32, 0.82)	
Study quality				
≥ 7	2 756 714	25 271	0.90 (0.78, 1.04)	0.026
< 7	391 545	24,815	0.60 (0.47, 0.77)	



CI, confidence interval (bars); VTE, venous thromboembolism; *, *P*-value for meta-regression

Figure 4: **Effect of statin therapy on venous thromboembolism in randomised controlled trials**

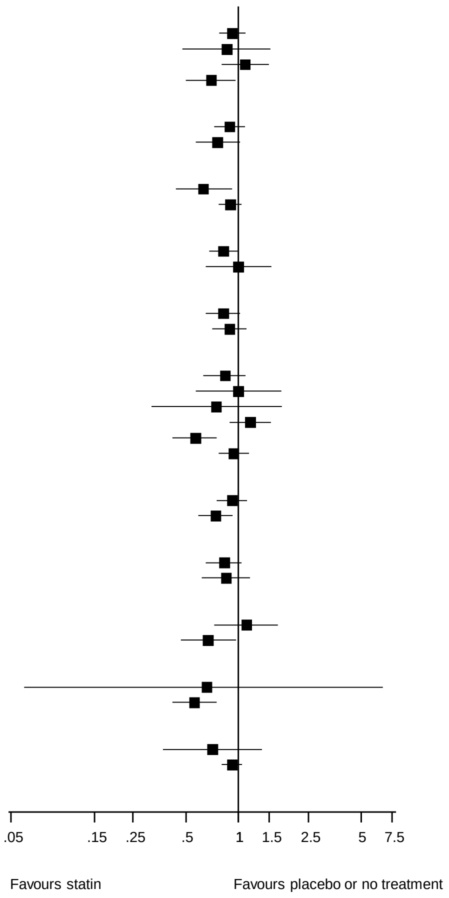
Author, year of publication	Statin group Events / Participants	Placebo group Events / Participants	RR (95% CI)
Venous thromboembolism			
Cowell, 2005	0 / 77	1 / 78	0.34 (0.01, 8.16
Crouse, 2007	1 / 700	0 / 281	1.21 (0.05, 29.5
Chan, 2010	0 / 134	1 / 135	0.34 (0.01, 8.17
Fassett, 2010	1 / 64	1 / 68	1.06 (0.07, 16.6
Feldman, 2010	2 / 314	1 / 326	2.08 (0.19, 22.7
Nakamura, 2006	3 / 3866	1 / 3966	3.08 (0.32, 29.5
Asselbergs, 2004	3 / 433	2 / 431	1.49 (0.25, 8.89
Sola, 2006	3 / 54	2 / 54	1.50 (0.26, 8.62
Knopp, 2006	4 / 948	10 / 916	0.39 (0.12, 1.23
GISSI-HF Investigators	9 / 2285	9 / 2289	1.00 (0.40, 2.52
Koren, 2004	9 / 1217	10 / 1225	0.91 (0.37, 2.22
Downs, 1998	9 / 3304	12 / 3301	0.75 (0.32, 1.78
Wanner, 2005	13 / 619	13 / 636	1.03 (0.48, 2.20
Sever, 2003	13 / 5168	20 / 5137	0.65 (0.32, 1.30
Colhoun, 2004	14 / 1428	26 / 1410	0.53 (0.28, 1.01
Kjeksus, 2007	15 / 2514	28 / 2497	0.53 (0.28, 0.99
Yusuf, 2016	14 / 6361	31 / 6344	0.45 (0.24, 0.84
Fellstrom, 2004	23 / 1050	23 / 1052	1.00 (0.57, 1.77
Freeman, 2011	28 / 2834	20 / 2865	1.42 (0.80, 2.52
SPARCL Investigators	34 / 2365	29 / 2366	1.17 (0.72, 1.92
Glynn, 2009	34 / 8901	60 / 8901	0.57 (0.37, 0.86
LIPID Study Group	79 / 4512	74 / 4502	1.07 (0.78, 1.46
HPS Study Group	168 / 10 269	178 / 10 267	0.94 (0.77, 1.16
Subtotal			0.85 (0.73, 0.99
Pulmonary embolism			
Glynn, 2009	17 / 8901	22 / 8901	0.77 (0.41, 1.45
Deep vein thrombosis			
Glynn, 2009	17 / 8901	38 / 8901	0.45 (0.25, 0.79



CI, confidence interval (bars); RR, relative risk

Figure 5: **Effect of statin therapy on venous thromboembolism in randomised controlled trials, grouped according to several study characteristics**

Subgroup	Statin group Events / Participants	Control group Events / Participants	RR (95% CI)	*P*-value*
Location				
Europe	248 / 23113	269 / 23113	0.92 (0.78, 1.10)	.150
North America	21 / 4709	25 / 4715	0.86 (0.48, 1.52)	
Asia-Pacific	83 / 8442	76 / 8536	1.09 (0.80, 1.49)	
Multinational	127 / 23153	182 / 22683	0.70 (0.50, 0.96)	
Design				
Double blind	257 / 34955	289 / 34545	0.89 (0.73, 1.09)	.419
Open label	222 / 24462	263 / 24502	0.76 (0.57, 1.02)	
Baseline population				
Primary prevention	47 / 16771	73 / 16449	0.63 (0.44, 0.92)	.109
Other	432 / 42646	479 / 42598	0.90 (0.77, 1.04)	
Baseline average age (years)				
≥ 60	438 / 50576	511 / 50108	0.82 (0.68, 0.99)	.455
< 60	41 / 8841	41 / 8939	1.00 (0.65, 1.54)	
Allocation concealment				
Adequate	283 / 36366	332 / 36449	0.82 (0.65, 1.02)	.641
Unclear	196 / 23051	220 / 22598	0.89 (0.71, 1.11)	
Statin class				
Artovastatin	93 / 12254	113 / 12216	0.84 (0.63, 1.10)	.015
Flavastatin	23 / 1050	23 / 1052	1.00 (0.57, 1.76)	
Lovastatin	9 to 3304	12 to 3301	0.75 (0.32, 1.77)	
Pravastatin	113 / 11645	97 / 11764	1.17 (0.89, 1.53)	
Rosuvastatin	73 / 20895	129 / 20447	0.57 (0.42, 0.75)	
Simvastatin	168 / 10269	178 / 10267	0.94 (0.77, 1.15)	
Duration (years)				
≥ 4	343 / 33892	368 / 33939	0.92 (0.75, 1.12)	.160
< 4	136 / 25525	184 / 25108	0.74 (0.59, 0.93)	
No. of events				
≥ 40	409 / 40234	469 / 40204	0.83 (0.65, 1.04)	.971
< 40	70 / 19183	83 / 18843	0.85 (0.62, 1.17)	
Artovastatin dosage (mg)				
> 20	45 / 3973	41 / 3995	1.11 (0.73, 1.68)	.081
≤ 20	48 / 8281	72 / 8221	0.67 (0.47, 0.97)	
Rosuvastatin dosage (mg)				
> 20	1 / 834	1 / 416	0.66 (0.06, 6.68)	.893
≤ 20	72 / 20061	128 / 20031	0.56 (0.42, 0.75)	
Type of data				
Published data	76 / 18096	111 / 18110	0.71 (0.37, 1.36)	.144
Previously unpublished data	403 / 41321	441 / 40937	0.92 (0.80, 1.05)	



CI, confidence interval (bars); VTE, venous thromboembolism; *, *P*-value for meta-regression

Table 1: **Summary characteristics of studies included in review**

	Observational cohort studies	Randomised controlled trials
Eligible studies		
No of studies	13	23
Median (IQR) follow-up (years)	4·6 (2·6-7·4)	3·9 (2·5-5·0)
Participants		
Total No of participants	3 148 259	118 464
Median (IQR) age (years)	61 (50-67)	62 (58-66)
Baseline population		
Primary prevention studies	7 (3 140 129)	4 (33 220)
Other studies	6 (8130)	19 (85 244)
Location		
Europe	8 (3 015 990)	8 (46 226)
North America	3 (129 725)	4 (9424)
Asia	2 (2544)	1 (7832)
Pacific	-	2 (9146)
Multinational	-	8 (45 836)
Outcome—No of studies (No of events)*		
Venous thromboembolism	12 (49 117)	23 (1031)
Deep vein thrombosis	2 (4513)	1 (55)
Pulmonary embolism	1 (3006)	1 (39)

IQR=interquartile range; values are number of studies (number of participants) unless stated otherwise;
*, are not unique studies or events

SUPPLEMENTARY MATERIAL

Appendix 1: PRISMA checklist

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	4
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	4
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Appendix 3
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	4-5
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	5
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	5
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	5-6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	6
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	6
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	6 and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	6-7, Appendices 4 and 5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	7, Appendix 6
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	7-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	7-10, Figures 2-5;

Section/topic	Item No	Checklist item	Reported on page No
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	10, Appendix 6
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Figures 3 and 5
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	10-11
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	13
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	None

Appendix 2: MOOSE checklist

Statins and venous thromboembolism: meta-analysis of prospective cohort and randomized intervention studies

Criteria		Brief description of how the criteria were handled in the review
Reporting of background		
√	Problem definition	Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is associated with significant morbidity and mortality. Statins have been suggested to have a protective effect on VTE outcomes, but the evidence is uncertain.
√	Hypothesis statement	Statin therapy has a protective effect on risk of VTE
√	Description of study outcomes	Venous thromboembolism, which includes deep vein thrombosis and pulmonary embolism
√	Type of exposure	Statin users
√	Type of study designs used	Prospective (cohort, case-cohort or “nested case control”) population-based studies and randomized controlled trials (RCTs)
√	Study population	Primary prevention populations and populations with pre-exsting disease
Reporting of search strategy should include		
√	Qualifications of searchers	Setor Kunutsor, PhD; Samuel Seidu, FRCP
√	Search strategy, including time period included in the synthesis and keywords	Time period: from inception of MEDLINE, EMBASE, Web of Science, and Cochrane databases to February 2016. The detailed search strategy can be found in Appendix 3.
√	Databases and registries searched	MEDLINE, EMBASE, and Web of Science
√	Search software used, name and version, including special features	Ovid was used to search EMBASE Reference Manager used to manage references
√	Use of hand searching	We searched bibliographies of retrieved papers and review papers
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list for excluded studies is available upon request.
√	Method of addressing articles published in languages other than English	We placed no restrictions on language
√	Method of handling abstracts and unpublished studies	We contacted several investigators for unpublished data and abstracts on the associations
√	Description of any contact with authors	We contacted authors who had conducted univariate or multivariate, but had not reported risk estimates
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the Methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, outcome, and possible effect modifiers of the association.
√	Assessment of confounding	We assessed confounding by ranking individual studies on the basis of different adjustment levels, and performed sub-group analyses to evaluate differences in the overall estimates according to levels of adjustment.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	For cohort studies, study quality was assessed based on the nine-star Newcastle–Ottawa Scale using pre-defined criteria namely: population representativeness, comparability (adjustment of confounders), ascertainment of outcome. Sensitivity analyses by several quality indicators such as study size, duration of follow-up, and adjustment factors. For RCTs, we used the Cochrane Collaboration’s risk of bias tool. This tool evaluates seven possible sources of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.
√	Assessment of heterogeneity	Heterogeneity of the studies was explored with I^2 statistic that provides the relative amount of variance of the summary effect due to the between-study heterogeneity.
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analyses, sensitivity analyses, meta-regression and assessment of publication bias are detailed in the methods. We performed random effects meta-analysis with Stata 14
√	Provision of appropriate tables and graphics	Table 1; Appendices 4 and 5; Figure 2-5
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 2 and 4
√	Table giving descriptive information for each study included	Table 1; Appendices 4 and 5
√	Results of sensitivity testing	Sensitivity analysis was conducted to assess the influence of each individual study by omitting one study at a time and calculating a pooled estimate for the remainder of the studies
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, I^2 values and

		results of sensitivity analyses
Reporting of discussion should include		
√	Quantitative assessment of bias	Sensitivity analyses indicate heterogeneity in strengths of the association due to most common biases in observational studies. The systematic review is limited in scope, as it involves published data. Individual participant data is needed. Limitations have been discussed.
√	Justification for exclusion	All studies were excluded based on the pre-defined inclusion criteria in methods section.
√	Assessment of quality of included studies	Brief discussion included in 'Methods' section
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	We discussed that potential unmeasured confounders may have caused residual confounding. Additionally, our findings could have been over-estimated somewhat due to preferential publication of extreme findings. The variations in the strengths of association may also be due to true population differences, or to differences in quality of studies.
√	Generalization of the conclusions	Discussed in the context of the results.
√	Guidelines for future research	We recommend analyses of individual participant data that would adjust consistently for potential confounders
√	Disclosure of funding source	No separate funding was necessary for the undertaking of this systematic review.

Appendix 3: MEDLINE literature search strategy

Relevant studies published from inception to May 12, 2016 (date last searched), were identified through electronic searches not limited to the English language using MEDLINE, EMBASE, Web of Science, and Cochrane databases. Electronic searches were supplemented by scanning reference lists of articles identified for all relevant studies (including review articles), and by hand searching of relevant journals. The computer-based searches combined search terms related to statins (e.g., *statin, hydroxymethylglutaryl-CoA reductase inhibitors, atorvastatin, simvastatin*) and outcomes (e.g., *venous thromboembolism, deep vein thrombosis, pulmonary embolism*) in humans, without any language restriction.

1 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or exp Anticholesteremic Agents/ or statin.mp. or exp Simvastatin/ (61633)
2 hmg.mp. (12976)
3 atorvastatin.mp. or exp Atorvastatin Calcium/ (7149)
4 lovastatin.mp. or exp Lovastatin/ (10452)
5 pravastatin.mp. or exp Pravastatin/ (4296)
6 cerivastatin.mp. (714)
7 fluvastatin.mp. (1775)
8 pitavastatin.mp. (658)
9 rosuvastatin.mp. or exp Rosuvastatin Calcium/ (2560)
10 venous thromboembolism.mp. or exp Venous Thromboembolism/ or exp Pulmonary Embolism/ or exp Thromboembolism/ (81522)
11 VTE.mp. or exp Venous Thrombosis/ (52065)
12 deep vein thrombosis.mp. or exp Venous Thrombosis/ (52544)
13 DVT.mp. (7458)
14 exp Pulmonary Embolism/ or PE.mp. (57751)
15 exp Embolism/ or embolism.mp. (82340)
16 thrombosis.mp. or exp Thrombosis/ (175624)
17 vein thrombosis.mp. (19742)
18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (71784)
19 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (269250)
20 18 and 19 (1025)
21 limit 20 to (humans) (737)

Each part was specifically translated for searching alternative databases.

Appendix 4: Characteristics of observational cohort studies included in meta-analysis

Lead author, publication year	Name of study or source of participants	Location of study	Study design	Baseline population	Year(s) of baseline survey	Baseline mean/median age (age range), years	% male	Duration of follow-up	Total no. of participants	No. of cases	Covariates adjusted for	Study quality
Ray, 2001	Ontario Provincial Healthcare Administrative Databases	Canada	Retrospective cohort	General population	1991-1999	72.9 (≥ 65)	NR	8.0	125,862	969	Age, sex, concurrent hospitalization or diagnosis of cancer, and concurrent prescription of aspirin, warfarin, or estrogen	6
Herrington, 2002	HERS	USA	Prospective cohort	Postmenopausal women with heart disease	NR	66.7 (NR)	0.0	4.1	2,763	41	Race, hypertension, diabetes mellitus, prior MI, creatinine clearance, LDL cholesterol, HDL cholesterol, and congestive heart failure.	7
Yang, 2002	UK GPRD	UK	Retrospective nested case-control	General population	1991-1999	NR (40-79)	NR	4.7	504	72	Age, calendar year, gender, smoking, BMI, estrogen use	6
Huerta, 2007	UK GPRD	UK	Prospective nested case-control	General population	1994-2000	63.0* (NR)	NR	4.8	16,550	6,550	Sex, age, calendar year, body mass index, smoking, cancer, fractures in the last month, surgery in the last 6 months, use of warfarin sodium, and visits to the family physician in the last year	7
Smeeth, 2009	THIN	UK	Prospective cohort	General population	1995-2006	NR (40-80)†	50.0	4.4	729,529	6,199	age, sex, propensity score, year of index date, first diagnosis of any of the following post-index date: diabetes, cerebrovascular disease, coronary heart disease, peripheral vascular disease, other atheroma, atrial fibrillation, heart failure, hyperlipidaemia, hypertension, other circulatory disease, cancer, dementia, first use of any of the following post-index date: aspirin, nitrates, fibrates, b-blockers, calcium channel blockers, potassium channel activators, diuretics, positive inotropes, anticoagulants, antihypertensives, or other cardiovascular drugs	8
Hippisley-Cox, 2010	QResearch Database	UK	Prospective cohort	General population	2002-2008	45.8 (30-84)	49.4	NR	2,004692	12,199	Age, BMI, smoking, tricyclic antidepressants, stage 3b+ kidney disease, rheumatoid arthritis, malabsorption, corticosteroids, SLE, depression, falls, asthma, cardiovascular disease, antipsychotic, any cancer, liver disease, peripheral vascular disease	7

Lead author, publication year	Name of study or source of participants	Location of study	Study design	Baseline population	Year(s) of baseline survey	Baseline mean/median age (age range), years	% male	Duration of follow-up	Total no. of participants	No. of cases	Covariates adjusted for	Study quality
Khemasuwan, 2011	Albert Einstein Medical Center	USA	Retrospective cohort	Patients with atherosclerosis	2005-2010	67.3 (NR)	50.2	1.1	1,100	107	Diabetes mellitus, smoking, cancer, metastatic cancer, immobilization, and use of estrogen hormone or its derivatives	6
Resh, 2011	Nephrology clinic	The Netherlands	Retrospective cohort	Patients with Nephrotic Syndrome	1995-2004	42.0 (> 18)	59.0	9.3	289	20	Age, sex, RAS inhibitors, diuretics, prednisolone, NSAIDS, acetysalicylic acid, vitamin K antagonists	6
Harbi, 2013	King Abdulaziz Medical City	Saudi Arabia	Prospective cohort	Critically ill patients	2006-2008	50.2 (≥ 18)	NR	30 days	798	6	Age, APACHE II score, GCS, creatinine, INR, aPTT, Trauma, femoral fracture, central line presence, malignancy, recent surgery, previous VTE, hemodialysis catheter use, use of graduated compression stocking, use of sequential compression device, DVT prophylaxis with unfractionated heparin or enoxaparin, and platelet transfusion	5
Fournier, 2014	UK GPRD	UK	Prospective nested case-control	Postmenopausal women	1987-2008	NR (50-79)	0.0	6.7	255,067	23,505	Matched for age, practice, duration of follow-up, calendar time; Adjusted for BMI, smoking, history of varicose veins treatment, inherited thrombophilia and screening for thrombophilia, antiphospholipid syndrome, immobilization, invasive surgical operation, trauma and fracture, myeproliferative disorders, cancer, IBD, nephroric syndrome, hypertension, CVD, use of tamoxifen and NSAID	6
Lassila, 2014	Health 2000 Survey	Finland	Retrospective cohort	General population	2000-2001	54.7 (≥ 30)	45.0	10.0	7,925	136	Age, sex, blood glucose lowering drug, insulin usage, vitamin K antagonists usage and antiplatelet agents usage	6
Lotsch, 2014	Vienna Cancer and Thrombosis Study	Austria	Prospective cohort	Patients with cancer	2003-2011	61.0 (NR)	55.9	2.0	1,434	107	antiplatelet drugs, biomarkers predictive for VTE (FVIII and sP-selectin), the variable high-risk or very high-risk site, age, BMI, diabetes and anamnestic myocardial infarction	7
Shai, 2014	Clalit Health Services Chronic Disease Registry	Israel	Prospective cohort	Patients with ovarian cancer	2000-2011	61.8 (18-90)	NR	3.1	1,746	175	Age, Charlson comorbidity Index, tumor stage, use of chemotherapy and aspirin use	7

*, For VTE patients; †, for statin users; APACHE, Acute Physiology and Chronic Health Evaluation; aPTT, activated partial thromboplastin time; BMI, body mass index; CVD, cardiovascular disease; DVT, deep vein thrombosis; GCS, Glasgow coma scale; GPRD, General Practice Research Database; HDL, high density lipoprotein; HERS, Heart and Estrogen/progestin Replacement Study; IBD, inflammatory bowel disease; INR, international normalized ratio; LDL, low density lipoprotein; MI, myocardial infarction; NR, not reported; NSAID, non-steroidal anti-inflammatory drugs; RAS, renin-angiotensin-system; SLE, systemic lupus erythematosus; VTE, venous thromboembolism

Appendix 5: Characteristics of clinical trials of statin therapy included in meta-analysis

Lead Author/Study, Publication Date	Name of study or source of participants	Study design	Patient population	Location	Baseline year of study	Age group	Males (%)	Allocation concealment	Blinding to subjects	Blinding to carers	Statin type, dosage	Duration of follow-up (years)	Completeness of follow-up (%)
Downs, 1988	AFCAPS/TexCAPS	Randomised, double blind	Primary prevention population	USA	1990-1993	45-73	85.0	Unclear	Yes	Yes	Lovastatin, 20-40 mg	5.3	100.0
LIPID study group, 1998	LIPID	Randomised, double blind	Patients with history of MI or unstable angina	Australia, New Zealand	1990-1992	31-75	83.0	Unclear	Yes	Yes	Pravastatin, 40 mg	5.6	NR
HPS study group, 2002	HPS	Randomised, open label	Patients with vascular disease or diabetes	UK	1994-1997	40-80	75.0	Yes	No	No	Simvastatin,, 40 mg	5.0	
Sever, 2003	ASCOT-LLA	Randomised, open label	Patients with hypertension plus other risk factors	Nordics, UK	1998-2000	40-79	81.0	Yes	No	No	Artovastatin, 10 mg	3.2	98.8
Fellstrom, 2004	ALERT	Randomised, double blind	Renal transplant patients	Multinational	NR	30-75	66.0	Unclear	Yes	Yes	Fluvastatin, 40 mg	5.1	NR
Colhoun, 2004	CARDS	Randomised, open label	Patients with type 2 diabetes and other risk factors	UK, Ireland	1997-2001	40-75	68.0	Yes	No	No	Artovastatin, 10 mg	3.9	99.3
Asselbergs, 2004	PREVEND IT	Randomised, double blind	Patients with microalbuminuria	Netherlands	1998-1999	28-75	65.0	Yes	Yes	Yes	Pravastatin, 40 mg	3.8	NR
Koren, 2004	ALLIANCE	Randomised, open label	Patients with CHD	USA	1995-1998	> 18	82.0	Unclear	No	No	Artovastatin, 10-80 mg	4.3	93.2
Cowell, 2005	SALTIRE	Randomised, double blind	Patients with calcific aortic stenosis	UK	2001-2002	> 18	70.0	Yes	Yes	Yes	Artovastatin, 80 mg	2.2	NR
Wanner, 2005	4D	Randomised, double blind	Diabetic hemodialysis patients	Germany	NR	18-80	54.0	Yes	Yes	Yes	Artovastatin, 20 mg	3.9	99.9
Knopp, 2006	ASPEN	Randomised, double blind	Patients with type 2 diabetes	Multinational	1996-1999	40-75	66.0	Unclear	Yes	Yes	Artovastatin, 10 mg	4.3	98.9

Lead Author/Study, Publication Date	Name of study or source of participants	Study design	Patient population	Location	Baseline year of study	Age group	Males (%)	Allocation concealment	Blinding to subjects	Blinding to carers	Statin type, dosage	Duration of follow-up (years)	Completeness of follow-up (%)
SPARCL Investigators, 2006	SPARCL	Randomised, double blind	Patients with stroke, TIA, or CHD	Multinational	NR	NR	60.	Unclear	Yes	Yes	Artovastatin, 80 mg	4.9	99.5
Sola, 2006	NR	Randomised, double blind	Patients with non-ischaemic HF and LVEF ≤ 35%	USA	NR	≥ 18	33.0	Unclear	Yes	Yes	Artovastatin, 20 mg	1.0	100.0
Nakamura, 2006	MEGA	Randomised, open label, blinded endpoint	Primary prevention population	Japan	1994-1999	40-70	30.0	Yes	No	No	Pravastatin, 10-20 mg	5.3	98.7
Kjeksus, 2007	CORONA	Randomised, open label	Patients with ischaemic HF	Multinational	NR	≥ 60	76.0	Yes	No	No	Rosuvastatin, 10 mg	2.7	NR
Crouse, 2007	METEOR	Randomised, double blind	Primary prevention population	Multinational	2002-2006	45-70	57.0	Unclear	Yes	Yes	Rosuvastatin, 40 mg	2.0	97.9
GISSI-HF Investigators, 2008	GISSI-HF	Randomised, double blind	Patients with CHF	Italy	2002-2005	≥ 18	77.0	Yes	Yes	Yes	Rosuvastatin, 10 mg	3.9	99.9
Glynn, 2009	JUPITER	Randomised, double blind	Primary prevention population	Multinational	2003-2006	≥ 50	61.8	Unclear	Yes	Yes	Rosuvastatin, 20 mg	1.9	NR
Feldman, 2010	LEADe	Randomised, double blind	Patients with mild to moderate Alzheimer’s disease	Multinational	NR	50-90	48.0	Yes	Yes	Yes	Artovastatin, 80 mg	1.5	70.6
Chan, 2010	ASTRONOMER	Randomised, double blind	Patients with mild to moderate aortic disease	Canada	2002-2005	18-82	61.0	Yes	Yes	Yes	Rosuvastatin, 40 mg	3.5	98.9
Fassett, 2010	LORD	Randomised, double blind	Patients with CKD	Australia	2002-2005	18-85	65.0	Yes	Yes	Yes	Artovastatin, 10 mg	2.5	62.9
Freeman, 2011	PROSPER	Randomised, double blind	Elderly at increased vascular risk	Scotland, Ireland, Netherlands	1997-1999	70-82	47.0	Yes	Yes	Yes	Pravastatin, 40 mg	3.2	100.0
Yusuf, 2016	HOPE-3 trial	Randomised, double blind	Participants at intermediate cardiovascular risk	Multinational	2007-2010	≥ 55	53.8	Yes	Yes	Yes	Rosuvastatin, 10 mg	5.6	99.1

AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALERT, Assessment of Lescol in Renal Transplant; ALLIANCE, Aggressive Lipid-Lowering Initiation Abates New Cardiac Events; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; ASPEN, Artovastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; ASTRONOMER, Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin; CARDS, Collaborative Artovastatin Diabetes Study; CORONA, Controlled Rosuvastatin in Multinational Trial in Heart Failure; CHF, congestive heart failure; CKD, chronic kidney disease; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insuffi cienza cardiac-Heart Failure; HF, heart failure; HOPE-3, Heart Outcomes Prevention Evaluation (HOPE)-3 trial, JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LEADe, Lipitor's Effect in Alzheimer's Dementia; LORD, Lipid Lowering and Onset of Renal Disease; LVEF, left ventricular ejection fraction; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; METEOR, Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin; NR, not reported; PREVEND IT, Prevention of Renal and Vascular Endstage Disease Intervention Trial; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; SALTIRE, Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TIA, transient ischaemic attack;

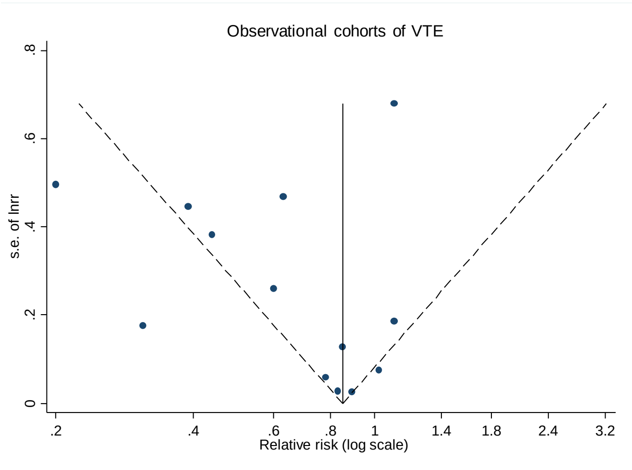
Appendix 6: Assessment of risk of bias

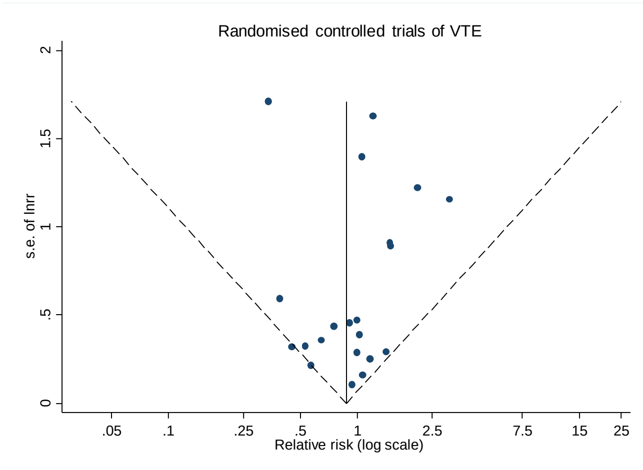
Trials	*Randon sequence generation*	*Allocation concealment*	*Blinding of participants & personnel*	*Blinding of outcome assessments*	*Incomplete outcome data*	*Selective reporting*	*Other bias*
PROSPER	+	+	+	+	?	+	+
JUPITER	+	?	+	?	+	+	+
AFCAPS/TexCAPS	+	?	+	+	?	+	+
LIPID	+	?	+	+	?	+	?
HPS	+	+	-	+	?	+	+
ASCOT-LLA	+	+	-	+	?	+	+
ALERT	+	?	+	?	?	+	?
CARDS	+	+	-	+	?	+	+
PREVEND IT	+	+	+	+	?	+	+
ALLIANCE	+	?	-	+	?	?	?
4D	+	+	+	+	?	+	+
SALTIRE	+	+	+	?	?	+	+
MEGA	+	+	-	+	?	+	+
ASPEN	+	?	+	+	?	+	+
SPARCL	+	?	+	?	?	+	+
CORONA	+	+	-	?	?	+	+
Sola, 2006	+	?	+	?	?	?	?
GISSI-HF	+	+	+	+	?	+	+
METEOR	+	?	+	?	?	+	?
LEADe	+	+	+	?	?	+	+
ASTRONOMER	+	+	+	?	?	+	+
LORD	+	+	+	?	?	+	+
HOPE-3	+	+	?	+	+	+	?

+	Low risk of bias
?	Unclear risk of bias
-	High risk of bias

Study acronyms in Appendix 5

Appendix 7: Assessment of small study effects by funnel plots and Egger's regression symmetry tests





The dotted lines show 95% confidence intervals around the overall summary estimate calculated using a fixed effect model; RCT, randomised controlled trial; VTE, venous thromboembolism *P*-value for bias calculated using Egger's test was 0.096 and 0.658 for observational cohorts and RCTs respectively.